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What Is Claimed Is:

1. A co-therapy for treating a cardiovascular disorder in a subject, wherein said co-therapy comprises  
5 administering a therapeutically-effective amount of an angiotensin converting enzyme inhibitor and administering an aldosterone antagonist in an amount therapeutically effective to antagonize aldosterone to  
10 reduce the death rate or the number of non-fatal hospitalizations as compared to monotherapy with an angiotensin converting enzyme inhibitor.
2. The co-therapy of Claim 1 further characterized by administering said angiotensin converting enzyme  
15 inhibitor and said aldosterone antagonist in a sequential manner.
3. The co-therapy of Claim 1 further characterized by administering said angiotensin converting enzyme  
20 inhibitor and said aldosterone antagonist in a substantially simultaneous manner.
4. The co-therapy of Claim 1 wherein said  
25 aldosterone antagonist is a spiro lactone-type compound.
5. The co-therapy of Claim 4 wherein said spiro lactone-type compound is spironolactone.
6. The co-therapy of Claim 1 wherein said  
30 angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate,  
35 temocapril, trandolapril, ceranapril, moexipril, quinaprilat, spirapril, Bioproject BP1.137, Chiesi CHF

1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat and Servier S-5590.

7. The co-therapy of Claim 6 wherein said  
5 angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate,  
10 temocapril, trandolapril, ceranapril, moexipril, quinaprilat and spirapril.

8. The co-therapy of Claim 1 further characterized by said angiotensin converting enzyme inhibitor and said  
15 aldosterone antagonist being used in said co-therapy in a weight ratio range from about 0.1-to-one to about twenty-five-to-one of said angiotensin converting enzyme inhibitor to said aldosterone antagonist.

20 9. The co-therapy of Claim 8 wherein said weight ratio range is from about 0.5-to-one to about fifteen-to-one.

10. The co-therapy of Claim 9 wherein said weight  
25 ratio range is from about 0.5-to-one to about five-to-one.

11. The co-therapy of Claim 9 wherein said  
30 angiotensin converting enzyme inhibitor is captopril, in a daily dose range from about 30 mg to about 80 mg per dose, or is enalapril in a dose range from about 5 mg to about 25 mg per dose.

12. The co-therapy of Claim 11 wherein said aldosterone antagonist is spironolactone in a daily dose range from about 1 mg to about 23 mg per dose.

5        13. The co-therapy of Claim 12 wherein said spironolactone daily dose is in a range from about 5 mg to about 20 mg.

10       14. The co-therapy of Claim 12 wherein said spironolactone daily dose is in a range from about 5 mg to about 15 mg.

15       15. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are  
20       administered at doses that in combination result in a statistically significant reduction in the death rate or the number of non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no  
25       substantial aldosterone antagonistic effect.

16. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an  
30       angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a  
35       statistically significant reduction in the death rate as

compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

5        17. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and  
10        wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the number of  
15        non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

20        18. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and  
25        wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the rate of  
30        deaths resulting from sudden death in subjects afflicted with or susceptible to elevated heart rate variability as compared to said combination therapy without the  
aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

35        19. A combination therapy for treating a cardiovascular disorder in a subject, wherein said

combination therapy comprises administering an  
angiotensin converting enzyme inhibitor, an aldosterone  
antagonist and a loop diuretic to the subject, and  
wherein the angiotensin converting enzyme inhibitor, the  
5 aldosterone antagonist and the loop diuretic are  
administered at doses that in combination result in a  
statistically significant reduction in the death rate  
for deaths resulting from progression of heart failure  
as compared to said combination therapy without the  
10 aldosterone antagonist, and wherein said loop diuretic  
has no substantial aldosterone antagonistic effect.

20. A combination therapy for treating a  
cardiovascular disorder in a subject, wherein said  
15 combination therapy comprises administering an  
angiotensin converting enzyme inhibitor, an aldosterone  
antagonist and a loop diuretic to the subject, and  
wherein the angiotensin converting enzyme inhibitor, the  
aldosterone antagonist and the loop diuretic are  
20 administered at doses that in combination result in a  
statistically significant reduction in the death rate or  
the number of non-fatal hospitalizations in subjects  
having a left ventricular ejection fraction greater than  
about 26% as compared to said combination therapy  
25 without the aldosterone antagonist, and wherein said  
loop diuretic has no substantial aldosterone  
antagonistic effect.

21. A combination therapy for treating a  
30 cardiovascular disorder in a subject, wherein said  
combination therapy comprises administering an  
angiotensin converting enzyme inhibitor, an aldosterone  
antagonist and a loop diuretic to the subject, and  
wherein the angiotensin converting enzyme inhibitor, the  
35 aldosterone antagonist and the loop diuretic are

administered at doses that in combination result in a statistically significant reduction in the death rate or the number of non-fatal hospitalizations in subjects having a left ventricular ejection fraction less than  
5 about 26% as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

10 22. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and  
15 wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination suppress clinically significant cough due to elevated pulmonary arterial fibrosis or low levels of pulmonary blood  
20 pressure in the subject as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

25 23. The combination therapy of Claim 22 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a statistically  
significant reduction in the death rate or the number of  
30 non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist.

24. A combination therapy for treating a cardiovascular disorder in a subject, wherein said  
35 combination therapy comprises administering a

therapeutically-effective amount of an angiotensin converting enzyme inhibitor, a therapeutically-effective amount of an aldosterone antagonist, a therapeutically-effective amount of a loop diuretic and a  
5 therapeutically-effective amount of digoxin to the subject.

25. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone  
10 antagonist, loop diuretic and digoxin are administered at doses that in combination result in a statistically significant reduction in the death rate as compared to the combination therapy of Claim 16.

15 26. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in a statistically significant reduction in the number of non-fatal  
20 hospitalizations as compared to the combination therapy of Claim 17.

27. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone  
25 antagonist, loop diuretic and digoxin are administered at doses that in combination result in a decrease in blood N-terminal atrial natriuretic factor level in the subject as compared to the combination therapy of Claim  
15.

30 28. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in a decrease in  
35 blood procollagen type III aminoterminal propeptide



5 level in the subject as compared to the combination  
therapy of Claim 15.

29. The combination therapy of Claim 24 wherein  
the angiotensin converting enzyme inhibitor, aldosterone  
10 antagonist, loop diuretic and digoxin are administered  
at doses that in combination result in an increase in  
left ventricular ejection fraction in the subject as  
compared to the combination therapy of Claim 15.

15 30. The combination therapy of Claim 15 wherein  
the subject is a human.

31. The combination therapy of Claim 15 wherein  
the subject is susceptible to sudden death.

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32. The combination therapy of Claim 15 wherein  
the subject is classified in New York Heart Association  
class III or class IV prior to combination therapy.

25 33. The combination therapy of Claims 15 wherein  
the subject has a left ventricular ejection fraction  
greater than about 26%.

34. The combination therapy of Claim 15 wherein  
30 the subject has a left ventricular ejection fraction  
less than about 26%.

35 35. The combination therapy of Claim 15 wherein  
the subject is susceptible to or suffering from  
clinically significant cough due to elevated pulmonary

5 arterial fibrosis or low levels of pulmonary blood pressure.

36. The combination therapy of Claim 15 wherein the loop diuretic is selected from furosemide and  
10 ethynacrylic acid.

37.. The combination therapy of Claim 15 further comprising the administration of a therapeutically-effective amount of digoxin.

15

38. The combination therapy of Claim 15 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a decrease in blood N-terminal atrial natriuretic factor level in the subject  
20 as compared to the combination therapy of Claim 15.

39. The combination therapy of Claim 15 wherein the angiotensin converting enzyme inhibitor, aldosterone  
25 antagonist and loop diuretic are administered at doses that in combination result in a decrease in blood procollagen type III aminoterminal propeptide level in the subject as compared to the combination therapy of Claim 15.

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40. The combination therapy of Claim 15 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a decrease in blood brain

5 natriuretic peptide level in the subject as compared to the combination therapy of Claim 15.

41. The therapy of Claim 15 further characterized by administering said angiotensin converting enzyme  
10 inhibitor, aldosterone antagonist and loop diuretic in a sequential manner.

42. The therapy of Claim 15 further characterized by administering said angiotensin converting enzyme  
15 inhibitor, aldosterone antagonist and loop diuretic in a substantially simultaneous manner.

43. The therapy of Claim 15 wherein said aldosterone antagonist is a spiro lactone-type compound.  
20

44. The therapy of Claim 15 wherein said spiro lactone-type compound is spironolactone.

45. The therapy of Claim 15 wherein said  
25 angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate,  
30 temocapril, trandolapril, ceranapril, moexipril, quinaprilat, spirapril, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat and Servier S-5590.

5        46.    The therapy of Claim 15 wherein said  
angiotensin converting enzyme inhibitor is selected from  
the group consisting of alacepril, benazepril,  
captopril, cilazapril, delapril, enalapril, enalaprilat,  
fosinopril, fosinoprilat, imidapril, lisinopril,  
10    perindopril, quinapril, ramipril, saralasin acetate,  
temocapril, trandolapril, ceranapril, moexipril,  
quinaprilat and spirapril.

15        47.    The therapy of Claim 15 further characterized  
by said angiotensin converting enzyme inhibitor and said  
aldosterone antagonist being used in said combination  
therapy in a weight ratio range from about 0.1-to-one to  
about twenty-five-to-one of said angiotensin converting  
enzyme inhibitor to said aldosterone antagonist.

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48.    The therapy of Claim 15 wherein said weight  
ratio range is from about 0.5-to-one to about fifteen-  
to-one.

25

49.    The therapy of Claim 15 wherein said weight  
ratio range is from about 0.5-to-one to about five-to-  
one.

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50.    The therapy of Claim 15 wherein said  
angiotensin converting enzyme inhibitor is captopril, in  
a daily dose range from about 30 mg to about 80 mg per  
dose, or is enalapril in a dose range from about 5 mg to  
about 25 mg per dose.

5        51.    The therapy of Claim 15 wherein said  
aldosterone antagonist is spironolactone in a daily dose  
range from about 1 mg to about 23 mg per dose.

10       52.    The therapy of Claim 15 wherein said  
spironolactone daily dose is in a range from about 5 mg  
to about 20 mg.

15       53.    The therapy of Claim 15 wherein said  
spironolactone daily dose is in a range from about 5 mg  
to about 15 mg.

54.    The method of Claim 15 wherein the aldosterone  
antagonist is an epoxy-steroidal aldosterone antagonist.

20       55.    The method of Claim 15 wherein the epoxy-  
containing compound has an epoxy moiety fused to the "C"  
ring of the steroidal nucleus of a 20-spiroxane  
compound.

25       56.    The method of Claim 15 wherein the 20-  
spiroxane compound is characterized by the presence of a  
9- $\alpha$ ,11- $\beta$ -substituted epoxy moiety.

30       57.    The method of Claim 15 wherein the epoxy-  
containing compound is selected from the group  
consisting of:

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-  
hydroxy-3-oxo-,  $\gamma$ -lactone, methyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

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Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid,  
10 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  $\gamma$ -lactone, (6 $\beta$ ,7 $\beta$ ,11 $\beta$ ,17 $\beta$ )-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, 7-(1-methylethyl) ester, monopotassium  
15 salt, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

20

3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  $\gamma$ -lactone, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ )-;

25 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid,  
30 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

5 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid,  
9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  $\gamma$ -lactone, (6 $\alpha$   
,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-  
10 hydroxy-3-oxo-,  $\gamma$ -lactone, ethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;  
and

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-  
hydroxy-3-oxo-,  $\gamma$ -lactone, 1-methylethyl ester, (7 $\alpha$ , 11  
15  $\alpha$ , 17 $\alpha$ )-.

58. The method of Claim 15 wherein the aldosterone antagonist is eplerenone.

20 59. The method of Claim 15 wherein the aldosterone antagonist is eplerenone in a daily dose range from about 0.5 mg to about 500 mg.

60. The method of Claim 15 wherein the aldosterone  
25 antagonist is an aldosterone antagonist other than spironolactone.

61. A composition comprising an angiotensin  
converting enzyme inhibitor, an aldosterone antagonist,  
30 a loop diuretic and digoxin, and the pharmaceutically acceptable salts, esters and prodrugs thereof.

62. A composition of Claim 63 comprising:

5        a first amount of an angiotensin converting enzyme inhibitor, or a pharmaceutically acceptable salt, ester or prodrug thereof;

      a second amount of an aldosterone antagonist, or a pharmaceutically acceptable salt, ester or prodrug  
10 thereof;

      a third amount of a loop diuretic, or a pharmaceutically acceptable salt, ester or prodrug thereof;

      a fourth amount of digoxin, or a pharmaceutically acceptable salt, ester or prodrug thereof; and  
15

      a pharmaceutically acceptable carrier;

      wherein the first, second, third and fourth amounts in combination comprise a therapeutically effective amount of said inhibitor, antagonist, loop diuretic and  
20 digoxin.

63.     A composition of Claim 64 wherein the aldosterone antagonist is spironolactone.

25     64.     A composition of Claim 64 wherein the aldosterone antagonist is eplerenone.